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Oxalyl amide assisted palladium-catalyzed synthesis of pyrrolidones *via* carbonylation of γ -C(sp³)-H bonds of aliphatic amine substrates†

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The first Pd-catalyzed regioselective γ -carbonylation of oxalyl amide protected aliphatic amines with carbon monoxide leading to synthesis of pyrrolidones has been developed. Both γ -methyl and cyclopropyl methylene C-H bonds are well activated to obtain the corresponding pyrrolidones in moderate to excellent yields. The role of 3-(trifluoromethyl)benzoic acid as an additive is critical as it helps in stabilizing the palladium intermediate formed during the catalytic cycle. The reaction scope is extended to benzylamine and allyl amine derivatives, thereby affording the corresponding products in good to excellent yields.

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Introduction

Recently, the development of practical methods for the construction of synthetically useful building blocks through direct C-H functionalization has emerged as an attractive and fruitful area in modern organic chemistry.¹ Among these methods, the transition-metal-catalyzed carbonylation of aryl C(sp²)-H bonds using CO as a carbon atom source to form an easily transformable carbonyl group has experienced landmark development.^{2–5} The first example was in the 1950s when Murahashi reported the cobalt-catalysed direct C-H functionalization/carbonylation of arenes with CO.⁶ In 1980, Fujiwara *et al.* also described a protocol involving Pd(OAc)₂-catalyzed direct carboxylation of some aromatic compounds with CO (15 atm) in an autoclave to give the corresponding carboxylic acids in poor to moderate yields.⁷ However, large excess of the arenes and lack of regioselectivity has hampered further application of this method in organic synthesis.

In the last decades, the challenge of selectivity in carbonylation of C(sp²)-H bonds has been overcome by the employment of directing groups,⁸ or where regioselectivity could also be achieved based on the substrates own intrinsic reactivity, *e.g.* amines,^{4*d*,8*d*,9} carboxylics,¹⁰ phenols,¹¹ and alcohols.¹² In spite of these great developments in the carbonylation of arenes, there is still limited success in the direct functionalization of

C(sp³)-H bonds with CO. In 2011, Chatani *et al.* described the Ru(0)-catalyzed regioselective carbonylation of unactivated C(sp³)-H bonds of aliphatic amides using bidentate directing groups (Scheme 1A). Similarly, Yu *et al.* reported the synthesis of succinimides *via* a Pd(II)-catalyzed β -carbonylation of aliphatic amide with CO (Scheme 1B).¹³ Recently, Gaunt *et al.* described a Pd-catalyzed carbonylation of secondary aliphatic amines at the β -position *via* a rarely reported four-membered palladacycle, leading to β -lactams in moderate to good yields (Scheme 1C).¹⁴ To the best of our knowledge, only these two examples of Pd-catalyzed carbonylation of C(sp³)-H bonds at specific positions have been reported. We speculated that during the catalytic cycle, Pd(II) might be easily reduced to Pd(0), thereby undergoing β -hydride elimination, and that there could be a competitive coordination with the palladium centre between CO and the specific C-H bond under CO atmosphere.¹⁵ For these reasons, the direct carbonylation of C(sp³)-H bonds remained a significant challenge.

In 2005, Daugulis and co-workers reported the first use of picolinamide and aminoquinoline auxiliaries as bidentate directing groups in Pd-catalyzed regioselective functionalization of C(sp³)-H bonds.¹⁶ Later, several groups demonstrated that these groups have an immense ability for enabling a wide variety of C-H transformation.¹⁷ Inspired by these results, our group has developed another bidentate directing group, oxalyl amide, which could be easily synthesized from oxalyl chloride and diisopropylamine *via* an S_N type reaction. We found that it could be used as a powerful directing group in enabling a variety of C-H transformations for both unactivated C(sp³)-H and C(sp²)-H bonds.¹⁸

In order to expand the reaction scope of oxalyl amide assisted C-H functionalization and explore its potential application towards transformation not achievable by other auxiliary-

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Scheme 1 Carbonylation of C(sp³)-H Bonds.

assisted C-H functionalization, we therefore proceeded to address the unreported γ -carbonylation of aliphatic amine substrates in a bid to synthesize important structural motifs of

pyrrolidones.¹⁹ Herein, we report a novel protocol for the preparation of pyrrolidones by Pd(II)-catalyzed γ -carbonylation of oxalyl amide protected aliphatic amine substrates. Both γ -methyl and cyclopropyl methylene C-H bonds were well activated and gave the corresponding pyrrolidones in moderate to excellent yields. Furthermore, pyrrolidones could be transformed into synthetically useful γ -amino acids under acidic conditions,²⁰ which offers a potential route towards synthesising unnatural amino acids (Scheme 1D). The substrate scope could also be further extended to oxalyl amide protected benzyl amine and allyl amine derivatives, affording the corresponding valuable synthons in good to excellent yields.

Results and discussion

We started our investigation with the reaction of oxalyl amide protected **1a** in the presence of Pd(OAc)₂ catalyst and silver acetate as oxidant under atmospheric pressure of CO at 140 °C in mesitylene for 24 h. Gratifyingly, the desired pyrrolidone **2a** was obtained in 22% yield. A variety of additives, such as AcOH, PivOH, (^{*n*}BuO)₂PO₂H, Ac-Gly-OH, which are well known to improve the reactivity of a palladium center, were applied to this reaction,²¹ with all of them displaying different levels of positive effect on the product yield. Pivalic acid greatly aided the conversion of **1a**, affording **2a** in 57% yield, but benzoic acid had a better promoting effect. However, further screening revealed that 3-(trifluoromethyl)benzoic acid was the most effective additive, with an excellent conversion of **1a** giving 85% yield of **2a**. During optimization studies, reactions with various different additives proceeded cleanly and it was observed that

Table 1 Optimization of palladium-catalyzed carbonylation of γ -C(sp³)-H bonds

Entry	Pd(OAc) ₂ (mol%)	Oxidant (2.5 equiv.)	Additive (0.3 equiv.)	Conv ^a (%)	Yield ^{a,b} (%)
1	10	AgOAc		26	22
2	10	AgOAc	AcOH	21	19
3	10	AgOAc	PivOH	60	57
4	10	AgOAc	(^{<i>n</i>} BuO) ₂ PO ₂ H	66	62
5	10	AgOAc	Ac-Gly-OH	12	8
6	10	AgOAc	PhCO ₂ H	76	75
7	10	AgOAc	<i>o</i> -PhPhCO ₂ H	27	18
8	10	AgOAc	<i>m</i> -CF ₃ PhCO ₂ H	87	85(83)
9	10	Ag ₂ CO ₃	<i>m</i> -CF ₃ PhCO ₂ H	21	20
10	10	Cu(OAc) ₂	<i>m</i> -CF ₃ PhCO ₂ H	2	0
11	10	BQ	<i>m</i> -CF ₃ PhCO ₂ H	5	4
12	0	AgOAc	<i>m</i> -CF ₃ PhCO ₂ H	2	0

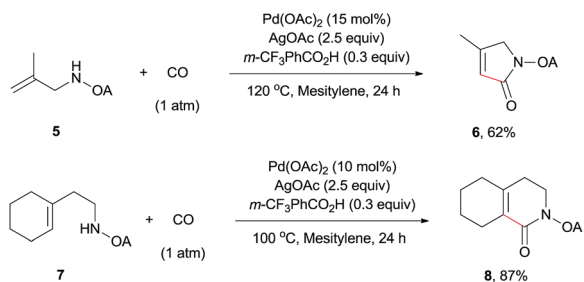
^a Reactions were carried out at 0.2 mmol scale under CO (1 atm), using mesitylene (0.3 mL) as the solvent; conversion and yield were based on GC using tridecane as the internal standard. ^b Isolated yield in parentheses. Ac = acetyl, Gly = glycine.



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Table 3 Palladium-catalyzed carbonylation of γ -C(sp²)-H bonds^a

^a Yields based on isolated products on a 0.2 mmol scale under CO (1 atm), using mesitylene (0.3 mL) as the solvent. ^b At 120 °C.



Scheme 2 Carbonylation of allylamine reaction.



Scheme 3 Scaling up and auxiliary removal.

under basic conditions at 50 °C, thus underlining the potential utility of this newly developed synthetic method.

Conclusion

In conclusion, we have developed the first Pd-catalyzed γ -carbonylation of oxalyl amide protected aliphatic amine substrates by using oxalyl amide as a bidentate directing group with AgOAc, and ArCO₂H under carbon monoxide atmosphere. This method is a novel strategy for the preparation of pyrrolidones. The substrate scope can be extended to benzylamine and allyl amine derivatives, giving products in good to excellent yields. The use of 3-(trifluoromethyl) benzoic acid is important for this transformation, and a detailed mechanistic study is now being undertaken in our laboratory.

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